REMARKS

Claims 1-4, 7-25, 28-32, and 62-65 are currently pending. Claims 1 and 65 have been amended. Support for the amended claims is found throughout the specification as originally filed, *inter alia*, in the following: page 34, lines 11-13. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

Claims 5-6, 26-27 and 33-61 have been canceled without prejudice or disclaimer as to the claimed subject matter pursuant to the restriction requirement or otherwise solely to expedite prosecution of the present application. Applicants reserve the right to pursue canceled subject matter in one or more continuation or divisional applications, as appropriate.

Claims 8-25 and 28-32 have been withdrawn as being drawn to non-elected subject matter. Applicants request rejoinder of these claims upon allowance of a linking claim.

Reply to Rejections under 35 U.S.C. § 102(b): **Sackstein**

Claim 1-4, 7, and 62-65 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Sackstein. (Blood 89:2773-2781 (1997)); "Sackstein"), as further evidenced by Dimitroff *et al.* (JBC 276: 47623-47631, 2001' "Dimitroff") and Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004; "Sackstein 2").

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicant respectfully submits that the disclosure of Sackstein fails to teach all the claim elements of the present claim. Specifically, Sackstein fails to disclose a purified preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans. That is, evening assuming, *arguendo*, that the polypeptide of Sackstein is the same as the recited polypeptide, the polypeptide of Sackstein was not purified. Sackstein describes a polypeptide that was not MECA-79 reactive and therefore was not immunoprecipitated from KG1a lysates

using a MECA-79 antibody. Sackstein therefore fails to disclose a preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans having the recited level of purity. Accordingly, Sackstein cannot anticipate the present claims because this reference, in the least, does not disclose a purified preparation of a glycosylated CD44 polypeptide wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide, as is recited in the claims. Furthermore, Sackstein does not teach a preparation comprising any polypeptide in the form of a sterile aqueous solution, sterile aqueous dispersions, or sterile powder.

Nothing disclosed in the other references cited by the Examiner as extrinsic evidence of anticipation (Dimitroff and Sackstein 2) changes these facts, nor do these references present any evidence to the contrary. Accordingly, Sackstein can not anticipate the present claims. Applicant requests that this rejection be withdrawn.

Reply to Rejections under 35 U.S.C. § 102(b): Stamenkovic

Claim 1-5, 7, 62-65 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Stamenkovic et al. (EMBO Journal 10:343-348, 1991); "Stamenkovic"). According to the Examiner Stamenkovic is prior art under 35 U.S.C. § 102 (b) because Stamenkovic teaches the isolation and source of CD44, including immunoprecipitation of CD44 derived form hematopoietic cells. Applicants disagree.

Stamenkovic teaches that there is an epithelial form of the CD44 polypeptide that is distinct from the hematopoietic/mesodermal form. Specifically, Stamenkovic describes that the epithelial form contains an additional extracellular peptide domain interposed proximal to the membrane-spanning domain and that this additional peptide sequence impairs binding to the extracellular matrix element hyaluronate. Stamenkovic demonstrates these two forms of CD44 by analysis of CD44 transcripts (i.e. RNA) from various cell types. (See Figure 2 in Stamenkovic) Figure 2 is a photograph on an RNA blot and does not indicate that any CD44 polypeptides were purified from any primary cell line.

Furthermore, Stamenkovic does not teach the isolation and source of native CD44 immunoprecipitated from hematopoietic cells as the examiner suggests. As stated in the specification, there are a myriad of CD44 isoforms and glycoforms and the examiner presents no

convincing evidence that the polypeptides of Stamenkovic are the same as those recited in the claims. At best, the rejection set forth on the Office Action is based on the principles of inherency in that the polypeptide of Stamenkovic is inherently the same as the recited polypeptide. Anticipation by inherency, however, requires that the prior art reference disclose each and every limitation of the claim.[1] Nowhere in Stamenkovic is a disclosure of a preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans having the recited level of purity. In order for a prior art reference to anticipate a claim under the principles of inherency, the prior art reference must ***necessarily*** function in accordance with, or include, all claimed limitations in order to anticipate the claim.[2] A conclusion that a result or characteristic ***may be present in the prior art reference is insufficient***, as provided by M.P.E.P. § 2112 as follows:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). (emphasis in original).

Additionally, as stated in *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, (Fed. Cir. 1995):

> Anticipation, however, requires identity of invention; the claimed invention, as described in appropriately construed claims, ***must be the same as that of reference***, in order to anticipate. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1267, 20 USPQ2d 1746, 1748 (Fed. Cir. 1991). See also In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ('the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it'). (33 USPQ2d at 1498)(emphasis added).

Applicant respectfully submits that Stamenkovic fails to inherently disclose a polypeptide that is ***necessarily*** a glycosylated CD44 polypeptide comprising an amino acid sequence encoded by a nucleotide sequence comprising exons 1-5, 16, 17, 18, and 20 of a human CD44 gene,

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[1] *See Standard Havens Prods., v Gencor Indus., Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991).

wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2, wherein the glycosylated CD44 polypeptide comprises sialylated, fucosylated glycans, wherein the glycosylated CD44 polypeptide is a ligand for E-selectin, L-selectin, or both, and wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide. Indeed, Figure 3 of Stamenkovic demonstrates immunoprecipitation of the "hematopoietic form" of CD44 (CD44H) from CD44H transfected COS cells. The COS cell line is derived from kidney cells of the African Green monkey. As is explained in Sako *et al.* (Cell. 1993 Dec 17;75(6):1179-86; Attached hereto) COS cells are known to lack relevant fucosyltransferases essential for producing the sialofucosylated selectin binding determinants of the claimed glycosylated polypeptide. Specfically, explains as follows:

> COS cells do not bind P-selectin nor do they possess the appropriate glycosylation apparatus to synthesize Lewis" (Le") or SLe", presumed carbohydrate components of a P-selectin ligand (Larsen et al., 1990; Polley et al., 1991).

Sako *et al.* at page 1179, right column, 4th line of the Results section; citations omitted. CD44H-transfected COS cells thus cannot produce the claimed glycosylated polypeptide as COS cells natively lack the relevant fucosysltransferase to create HCELL.

Moreover, none of the CD44 isoforms described in Stamenkovic have the same molecular weight profile as the species exhibiting L-selectin ligand activity. As is described in the specification at Example 4: *Identification and Characterization of HCELL* (page 17), the major L-selectin ligand activity can be found at 98 kD species. Stamenkovic does not disclose this species. Accordingly, the CD44 isoforms identified by Stamenkovic cannot be the same as those presently claimed.

Accordingly, Stamenkovic cannot anticipate the present claims because this reference, in the least, does not necessarily disclose a purified preparation of a glycosylated CD44 polypeptide wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide, as is recited in the claims. Furthermore, Stamenkovic does not teach a preparation comprising any polypeptide in the form of a sterile aqueous solution, sterile aqueous dispersions, or sterile powder.

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[2] *See In re King,* 801 F.2d 1324, 1326 (Fed. Cir. 1986).

In view of the above, Applicant requests that this rejection be withdrawn.

Reply to Rejections under 35 U.S.C. § 102(b): **Dougherty**

Claims 1-4, 7, and 62-65 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Dougherty *et al.* (J. Exp. Med. 174: 1-5 (1991)); "Dougherty"). Dougherty discloses CD44 isoforms named by the authors as CD44R1 and CD44R2. Dougherty, however, fails to disclose forms of these polypeptides that comprise sialylated, fucosylated glycans. As stated in the specification, there are a myriad of CD44 isoforms and glycoforms and the examiner presents no convincing evidence that the polypeptides of the Dougherty are the same as those recited in the claims. At best, the rejection set forth on the Office Action is based on the principles of inherency in that the polypeptide of Dougherty is inherently the same as the recited polypeptide. Anticipation by inherency, however, requires that the prior art reference disclose each and every limitation of the claim.[3] Nowhere in Dougherty is a disclosure of a preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans having the recited level of purity. In order for a prior art reference to anticipate a claim under the principles of inherency, the prior art reference must ***necessarily*** function in accordance with, or include, all claimed limitations in order to anticipate the claim.[4] A conclusion that a result or characteristic ***may be present in the prior art reference is insufficient***, as provided by M.P.E.P. § 2112 as follows:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). (emphasis in original).

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[3] *See Standard Havens Prods., v Gencor Indus., Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991).
[4] *See In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986).

Additionally, as stated in *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, (Fed. Cir. 1995):

> Anticipation, however, requires identity of invention; the claimed invention, as described in appropriately construed claims, ***must be the same as that of reference***, in order to anticipate. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1267, 20 USPQ2d 1746, 1748 (Fed. Cir. 1991). See also In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ('the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it'). (33 USPQ2d at 1498)(emphasis added).

Applicant respectfully submits that Dougherty fails to inherently disclose a polypeptide that is ***necessarily*** a glycosylated CD44 polypeptide comprising an amino acid sequence encoded by a nucleotide sequence comprising exons 1-5, 16, 17, 18, and 20 of a human CD44 gene, wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2, wherein the glycosylated CD44 polypeptide comprises sialylated, fucosylated glycans, wherein the glycosylated CD44 polypeptide is a ligand for E-selectin, L-selectin, or both, and wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide. Indeed, as evidenced by the data of molecular weight, the CD44 molecules described in Dougherty are indeed different than those currently described in the specification. On page 2, 2nd column, 1st paragraph of the Results and Discussion section, Dougherty clearly indicates that the identified CD44 isoforms have a molecular weight of approximately 115 and 130 kD. As is described in the specification at Example 4: *Identification and Characterization of HCELL* (page 17), the major L-selectin ligand activity can be found at 98 kD species. Dougherty does not disclose this species. Accordingly, the CD44 isoforms identified by Dougherty cannot be the same as those presently claimed.

Accordingly, Dougherty cannot anticipate the present claims because this reference, in the least, does not necessarily disclose a purified preparation of a glycosylated CD44 polypeptide wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide, as is recited in the claims. Furthermore, Dougherty does not teach a preparation comprising any polypeptide in the form of a sterile aqueous solution, sterile aqueous dispersions, or sterile powder.

In view of the above, Applicant requests that this rejection be withdrawn.

Reply to Rejections under 35 U.S.C. § 103(a): **Sackstein/Stamenkovic/Dougherty/Ni/McEver**

Claims 1-4, 7, and 62-65 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Sackstein, Stamenkovic, and/or Dougherty (explained above), in view of Ni *et al.* (U.S. Patent No. 5,942,417; "Ni") and McEver *et al.* (U.S. Patent No. 6,124,267; "McEver"). Applicants disagree with this rejection for the reasons below.

Sackstein discloses a glycoprotein L-selectin ligand express in KG1a cells that possess functional properties that overlap with the CD44 glycoprotein now claimed. Sackstein, however, fails to disclose a purified preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans. Evening assuming, *arguendo*, that the polypeptide of Sackstein is the same as the recited polypeptide, the polypeptide of Sackstein was not purified. Sackstein describes a polypeptide that was not MECA-79 reactive and therefore was not immunoprecipitated from KG1a lysates. Sackstein therefore fails to disclose a preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans having the recited level of purity.

Stamenkovic and Dougherty also fail to disclose the a purified preparation of a glycosylated CD44 polypeptide comprising, *inter alia*, sialylated, fucosylated N-glycans. The examiner relies on the principles of inherency to apply these references to the instant claims. As is explained above, these references fail to disclose a purified preparation of a CD44 isoform necessarily having all of the elements of the claims.

The Examiner cites Ni and McEver to support the argument that one of ordinary skill in the art would have utilized the protein purification techniques disclosed in these references to isolate the ligand identified in Sackstein. For example, the examiner relied on Ni for its teaching of methods of isolating and expressing isolated proteins of interest, wherein "isolated encompasses remov[al] from its native environment, purified and produced by recombinant means." See Office Action at page 12. Sackstein, however, fails to sufficiently and specifically identify the ligand described therein to a degree that would permit a person of ordinary skill in the art to remove the ligand from its native environment, purify, and produce the ligand by recombinant means. For example, Sackstein fails to provide the amino acid sequence of the

ligand that would permit the recombinant expression of the ligand. Accordingly, the combination of Sackstein and Ni would fail to produce the preparation of the claims.

The Examiner cites McEver for its disclosure that "the known manipulation and expression of interest that are associated with sialyated and fucosylated glycan and that interact with selectins." See Office Action at page 13, fist paragraph. The examiner specifically cites the columns 9-11 and 15-44, which provide guidance for the isolation and purification of recombinant proteins. As discussed above, however, Sackstein, fails to sufficiently and specifically identify the ligand described therein to a degree that would permit a person of ordinary skill in the art to recombinant lyexpress the ligand. For example, Sackstein fails to provide the amino acid sequence of the ligand that would permit the recombinant expression of the ligand. Accordingly, the combination of Sackstein and McEver would fail to produce the preparation of the claims.

To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03. The primary references of Sackstein, Stamenkovic, and/or Dougherty fail to disclose or suggest at least one of the elements recited in the claims, as mentioned above. The Office Action does not rely on the secondary references to cure the deficiencies of the primary references, which forces the conclusion that the combination of the prior art references would not teach every element of the claims and therefore fails to render obvious the present claims. As such, applicant respectfully submits that the rejection fails to establish a *prima facie* case of obviousness.

CONCLUSION

Applicants believe that this case is in condition for allowance. If the Examiner has any questions, the Examiner is invited to contact the undersigned by telephone.

Respectfully submitted,

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